

# Impairment of diastolic function during short-term anthracycline chemotherapy

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## Abstract

**Objective**—To assess the early changes in left ventricular diastolic and systolic function due to anthracycline treatment.

**Design**—A prospective study of cardiac function by radionuclide angiography in adults before and one month after the end of anthracycline treatment.

**Patients**—60 patients without cardiac disease treated with chemotherapy containing anthracycline.

**Methods**—Cardiac function was assessed by radionuclide measurement throughout treatment. Ejection fraction, peak ejection rate, time to peak ejection rate, filling rate, and time to peak filling rate were measured before and after treatment. To normalise radionuclide measurements of the left ventricular diastolic function the ratio of the filling rate to the ejection fraction and the ratio of the filling rate to the peak ejection rate were calculated.

**Results**—No patient developed symptomatic congestive cardiac failure. The ejection fraction decreased from 58% (5%) to 55% (6%) ( $P < 0.001$ ), the peak ejection rate fell from 2.99 (0.41) to 2.77 (0.41) of the end diastolic volume per second ( $P < 0.001$ ), and the peak filling rate from 2.71 (0.47) to 2.55 (0.44) of the end diastolic volume per second ( $P < 0.01$ ) after treatment. No difference was observed in the normalised ratios.

**Conclusions**—This report shows simultaneous impairment of left ventricular systolic and diastolic radionuclide parameters. The absence of variation in normalised measurements suggests similar changes in ejection fraction, peak ejection rate, and peak filling rate throughout treatment.

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**Keywords:** anthracycline cardiotoxicity, diastolic function, radionuclide angiography.

Anthracyclines are effective anticancer agents against various solid tumours and haematological malignancies, but their therapeutic value is limited by their myocardial toxicity.<sup>1-3</sup> Patients at high risk of congestive heart failure must be detected. Serial radionuclide determination of the left ventricular ejection fraction can provide advanced warning of cardiotoxicity caused by doxorubicin

hydrochloride before clinical signs of left ventricular dysfunction have developed. From studies based on limited groups of patients it has been suggested that diastolic impairment of the left ventricle could occur before the ejection fraction drops.<sup>4,5</sup> To determine whether impaired left ventricular diastolic or systolic function is a more relevant sign of anthracycline cardiotoxicity, a prospective study was performed using radionuclide angiography before any treatment and four weeks after the end of chemotherapy.

## Patients and methods

Sixty consecutive patients without clinical manifestations of cardiac disease, in particular no hypertension or ischaemic symptoms (normal chest radiograph and normal electrocardiogram), were studied before the first dose of anthracycline. No patient had had mediastinal irradiation. Thirty six women and twenty four men were included; their mean age was 50 (12) years (range 23-72) and there was an even distribution of ages through each decade. All patients underwent routine gated heart angiography before starting chemotherapy for lymphoma (10 patients), leukaemia (22), or breast carcinoma (28).

## DRUG REGIMENS

Patients received different anthracyclines, and the doses were expressed as an equivalent therapeutic dose of doxorubicin (DXR).<sup>6</sup> The doses ranged from 75 to 550 mg/m<sup>2</sup> of body surface area (mean 251 (111) mg/m<sup>2</sup>). No patient developed clinical evidence of heart failure. Drug toxicity was not assessed in an endomyocardial biopsy specimen because biopsy is necessary only when doses are greater than 550 mg/m<sup>2</sup> or in patients at risk.<sup>2</sup>

## PROTOCOL

Two gated radionuclide angiograms were obtained for each patient. The first was obtained before the start of treatment, the second one month after completion of the chemotherapy.

## RADIONUCLIDE ANGIOGRAPHY

Radionuclide angiography was performed while patients were lying supine. The blood pool was labelled with technetium-99m (740 MBq (20 mCi)). Data were acquired in the left anterior oblique view that showed the best separation between right and left ventricles when a Philips gamma camera with a small field of view and general purpose collimator

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Table 1 Correlation coefficients for left ventricular parameters before anthracycline chemotherapy in 60 patients

	Peak filling rate (EDV/s)	Peak ejection rate (EDV/s)	Peak filling rate (SV/s)	Peak ejection rate (SV/s)	Ratio of peak filling to peak ejection rate
Age (years)	-0.428***	0.201	-0.578***	0.036	-0.573***
Heart rate (beats/min)	0.460***	0.560***	0.518***	0.709***	0.001
Ejection fraction (%)	0.267*	0.468***	0.274*	-0.235	-0.102

\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001.

was used. The camera had an interface with a Sopha P512 computer. Images of 6 million counts were obtained using 32 frames and a  $64 \times 64$  matrix with a pixel size of 2.4 mm.

RR intervals and heart rate (beats/min) were recorded. Cardiac cycles with RR intervals that were not within 10% of the average value were discarded. Left ventricular ejection fraction at rest was determined by manual definition of end diastolic and end systolic regions. The background region was also manually defined outside the end systolic boundary extending around the apex and along the lateral wall of the left ventricle. The first degree derivative curve was calculated by convolution of the curve of left ventricular volume by using a derivative filter of five points. To analyse systolic function we calculated the peak ejection rate, and the time to the peak, and for diastolic function the peak filling rate and the time to the peak. The peak rates were expressed as a fraction of the end diastolic volume (EDV/s) and as a fraction of stroke volume (SV/s). To minimise the contribution of systole to the peak filling rate we also expressed the peak filling rate as a fraction of peak ejection rate.<sup>7,8</sup>

### Statistics

Parameters before and after treatment were compared by the paired Student's *t* test. The relations of peak filling rate, peak ejection rate, and their ratio to age, heart rate, and left ventricular ejection fraction were determined by calculation of Pearson correlation coefficients. P values of less than 0.05 were considered significant.

Multiple regression analysis was carried out for filling parameters that correlated significantly with age, heart rate, and left ventricular ejection fraction. The standard error of the estimate (SEE) was calculated for each regression to indicate the spread of the results. The fractional standard error was also calculated

as SEE/mean, enabling a direct comparison of the goodness of the fit for different parameters. Estimates of error variance for the filling parameters were directly compared. The significance of the variation in ejection fraction versus the variation in the peak filling rate was tested by a  $\chi^2$  test.

### Results

#### BEFORE CHEMOTHERAPY

Before chemotherapy both filling and ejection parameters correlated with heart rate and ejection fraction, whereas only the filling parameters were related to age (table 1). The dependence of the peak filling rate (EDV/s) on heart rate, age, and ejection fraction was described by the multiple regression equation in table 2. In contrast, when peak filling rate was expressed as SV/s it depended only on heart rate and age. Ultimate normalisation of the peak filling rate to peak ejection rate showed a dependence on age only, thus eliminating the contribution of the heart rate and of the ejection fraction (table 2).

The alteration in diastolic function with age was reflected by a significant negative correlation ( $P < 0.001$ ) with the normalised filling parameters. Conversely, for the ejection fraction, Pearson correlation coefficient was significant for peak filling rate ( $r = 0.267$ ,  $P < 0.05$ ) but not for age ( $r = 0.245$ ,  $P = 0.06$ ) and heart rate ( $r = -0.142$ ,  $P = 0.28$ ). The regression equation before chemotherapy was: ejection fraction =  $49.008 + 3.143 \times$  peak filling rate ( $P < 0.05$ ).

#### AFTER CHEMOTHERAPY

After chemotherapy heart rate did not change significantly whereas left ejection fraction and peak ejection rate were significantly decreased ( $P < 0.001$  and  $P < 0.01$ , respectively). The time to peak ejection rate increased significantly ( $P < 0.02$ ) (table 3).

Peak filling rate (EDV/s) showed a significant decrease after chemotherapy ( $P < 0.01$ ), without modification of the time to reach the peak rate (table 3). Peak filling rate (SV/s) and the normalised parameter of diastolic function (ratio of peak filling to ejection rates) did not change after chemotherapy (table 3).

The change in peak filling rate and the change in ejection fraction were significantly correlated ( $r = 0.466$ ,  $P < 0.001$ ) (figure 1). The decrease in peak filling rate and the decrease in peak ejection rate were also correlated ( $r = 0.495$ ,  $P < 0.001$ ) (figure 2). Forty four patients had a parallel change in ejection fraction and peak filling rate ( $\chi^2 = 7.42$ ,  $P < 0.01$ ). Ejection fraction was also dependent

Table 2 Multiple regression analysis for filling parameters before anthracycline chemotherapy in 60 patients. Values are standard errors of estimate (fractional standard errors)

	Peak filling rate (EDV/s)	Peak filling rate (SV/s)	Ratio of peak filling to peak ejection rate
Age	0.425 (0.157)	0.663 (0.140)	0.132 (0.144)
Age + heart rate	0.359 (0.133)	0.484 (0.103)	—
Age + heart rate + ejection fraction	0.283 (0.104)	—	—

EDV/s, end diastolic volume per second; SV/s, stroke volume per second.

Peak filling rate (EDV/s) =  $-0.0222 \times$  age +  $0.0204 \times$  heart rate +  $0.0420 \times$  ejection fraction -  $0.2657$  ( $P < 0.001$ ).

Peak filling rate (SV/s) =  $-0.0401 \times$  age +  $0.035 \times$  heart rate +  $3.9111$  ( $P < 0.001$ ).

Ratio of peak filling to peak ejection rate =  $-0.0074 \times$  age +  $1.2841$  ( $P < 0.001$ ).

**Table 3** Variables before and after anthracycline chemotherapy in 60 patients. Values are means (SD)

	Before	After	P value
R/R interval (ms)	750 (115)	774 (120)	NS
Heart rate (beats/min)	82 (13)	79 (12)	NS
Ejection fraction (%)	57 (5)	55 (6)	<0.001
Ejection rate:			
Peak (EDV/s)	2.99 (0.41)	2.77 (0.41)	<0.001
Time to peak (ms)	147 (24)	158 (26)	<0.02
Filling rate:			
Peak (EDV/s)	2.71 (0.47)	2.55 (0.44)	<0.01
Time to peak (ms)	165 (61)	162 (59)	NS
Peak (SV/s)	4.73 (0.80)	4.67 (0.81)	NS
Ratio of peak filling to peak ejection rate	0.91 (0.16)	0.93 (0.15)	NS

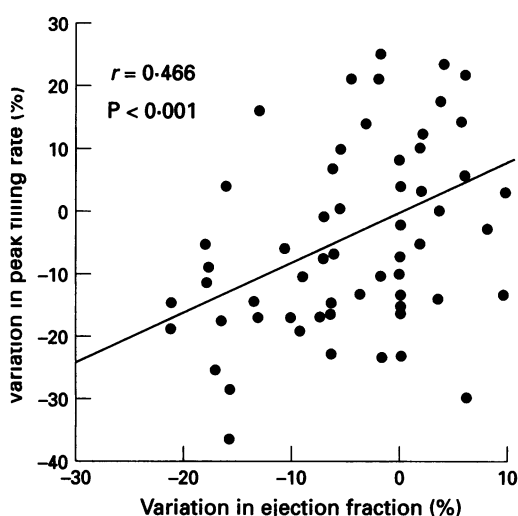
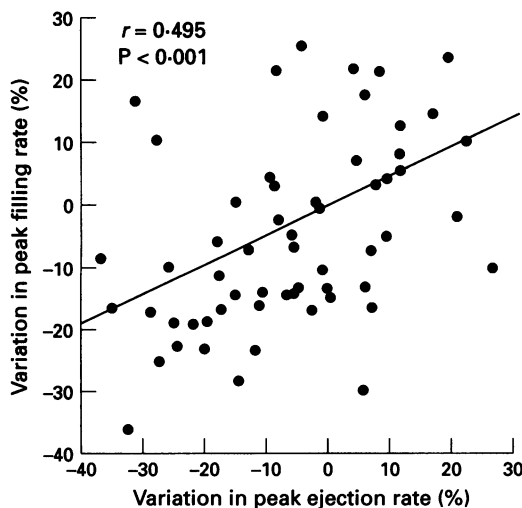
\*Paired *t* test.

EDV/s, end diastole volume per second.

SV/s, stroke volume per second.

on peak filling rate ( $r = 0.358$ ,  $P < 0.005$ ); the regression equation was: ejection fraction =  $43.229 + 4.514 \times$  peak filling rate ( $P < 0.005$ ).

No correlation was found between the

**Figure 1** Percentage variation in peak filling rate versus percentage variation in ejection fraction before and after anthracycline chemotherapy in 60 patients.**Figure 2** Percentage variation in peak filling rate versus percentage variation in peak ejection rate before and after anthracycline chemotherapy in 60 patients.

doxorubicin dose and variation in diastolic or systolic parameters ( $r = 0.002$ ,  $P = 0.98$  for ejection fraction *v* dose;  $r = 0.125$ ,  $P = 0.34$  for peak filling rate *v* dose).

## Discussion

### INTERRELATION BETWEEN SYSTOLIC AND DIASTOLIC INDICES

Our results are similar to those of Lee *et al* on almost the same number of normal patients in terms of the filling parameters and age, heart rate, and ejection fraction and the dependence of the normalised radionuclide measurements of left ventricular diastolic function on age.<sup>7</sup> We also confirmed the influence of the filling parameters on the left ventricular systolic function before any treatment. This is in accordance with both angiographic studies and studies of isolated cardiac myocytes, which have shown that diastolic function is necessary to maintain systolic performance.<sup>9,10</sup>

The absence of variation in age and heart rate, which greatly influence the filling parameters, permitted a good study of the relation between changes in diastolic and systolic function.<sup>7</sup> Moreover, we did not study patients with hypertension and coronary artery disease as they are known to have abnormalities of relaxation or to have reduced distensibility.<sup>9</sup>

### INFLUENCE OF ANTHRACYCLINES ON SYSTOLIC AND DIASTOLIC INDICES

Several studies have suggested that the early impairment in heart function during anthracycline toxicity could be a diastolic dysfunction. This has been supported by radionuclide studies or echographical studies on limited groups of patients—namely, 12 and 35 patients.<sup>4,5</sup> Our results are in agreement with those of previous studies, which found no correlation between low doses of anthracycline and change in diastolic or systolic parameters.<sup>5</sup>

Our study confirms the previously observed diastolic dysfunction. In a large group of patients the peak filling rate dropped by 6% after treatment, without any significant change in the time to peak filling rate, but our results showed simultaneous impairment of left ventricular function during systole in contrast to the studies of Lee *et al* and Marchandise *et al*.<sup>4,5</sup> The peak filling rate expressed as stroke volume per second and the ratio of peak filling to ejection rates were unchanged after treatment, which is evidence of the interdependence of the systolic and diastolic changes. The correlation between ejection fraction and peak filling rate further confirms that both changes were parallel indices of the same pathological process. The correlation between ejection fraction and peak filling rate suggests that the diastolic dysfunction due to anthracycline cardiotoxicity affects systolic function.

The perfusion of doxorubicin hydrochloride through isolated rat hearts increases coronary resistance, which could result from a direct coronary vasoconstriction or from an

alteration in ventricular compliance with compression of intramural arteries.<sup>11</sup> Pelikan *et al* suggest that diastolic changes in the properties of the ventricles are consistent with a decrease in compliance. The effects of coronary factors (coronary arterial and venous pressures, coronary blood volume and flow) are sufficiently large to explain the haemodynamic abnormalities of the distensibility of the left ventricle during the acute phase. We studied patients one month after the completion of chemotherapy, when the direct effect of anthracyclines on the coronary factors is unlikely to explain the results.

Some physiopathological data, however, support the hypothesis of myocardial oedema, which could account for reduced compliance of the left ventricle as a result of free radical generation or calcium homeostasis. Lipid peroxidation induced by doxorubicin hydrochloride has been observed in several *in vitro* and *in vivo* studies,<sup>12-14</sup> the ability of anthracyclines to form superoxide anions is due to NADH dehydrogenase and NADPH cytochrome P-450 reductase.<sup>15</sup> Another possible mechanism of this cardiotoxicity could be the calcium overload resulting from the augmentation of the slow inward calcium current and calcium influx.<sup>16,17</sup> The alteration of myocardial calcium homeostasis is intimately related to radical mediated reactions, including lipid peroxidation.<sup>13</sup> The increased lipid peroxidation could be associated with changes in the permeability of cell membranes and thus to the observed myocardial oedema.<sup>18,19</sup> The distensibility of the heart muscle was decreased in proportion with the accumulation of oedema fluid; this change of myocardial distensibility became noticeable whenever fluid accumulation amounted to 4-5% of the original heart weight.<sup>20</sup>

During long term anthracycline cardiotoxicity in patients with chronic heart failure the results of haemodynamic studies suggest restrictive endomyocardial disease as a result of the endomyocardial fibrosis.<sup>21</sup> In our patients oedema is more likely than fibrosis to be the cause because of the time between the two studies and also the moderate parallel changes in systolic and diastolic function. Only analysis of endomyocardial biopsy specimens coupled with a precise technique to measure tissue water content could have separated these two possible mechanisms. Nevertheless, some patients had discordant variations in systolic and diastolic function, but the proportion was not significant. This fact could explain why previous studies based on a small number of subjects have found differences between diastolic and systolic responses to anthracycline chemotherapy.

#### CONCLUSION

We found evidence of impaired left ventricular diastolic and systolic function in a large group of patients receiving anthracycline. The absence of variation in normalised parameters

and the correlation between peak filling rate and ejection fraction confirmed the interdependence between the ejection and filling parameters during the early stage of anthracycline treatment. Further studies are needed to establish whether this relation persists to the time when chronic histological damage is more likely to occur.

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